QSAR and 3D-QSAR analysis of structurally diverse ALS inhibitors: sulfonylureas and triazolopyrimidine-2-sulfonamides

Guangfu Yang,[1]* Huayin Liu[2] and Huazheng Yang[2]

[1]*Institute of Organic Synthesis, Central China Normal University, Wuhan 430079, P R China*
[2]*Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P R China*

Abstract: For the purpose of better understanding the molecular mechanism of action of sulfonylurea and sulfonamide herbicides, the quantitative relationship between their structure and herbicidal activity against rape, *Brassica campestris* L, was analysed using physicochemical parameters and regression analysis and comparative molecular field analysis (CoMFA). The results showed that the structure–activity relationships of the two sets of compounds were identical, which suggested that the two different sets of compounds affect a common region of the receptor site. The CoMFA results were consistent with those derived from traditional QSAR analysis. Combining the traditional QSAR analysis with the CoMFA results, we can conclude that the variations in the herbicidal activity of the two sets of ALS inhibitors were governed dominantly by the three-dimensional steric and electrostatic field parameters of molecules participating in the interaction with the receptor site and there is apparently an optimum electronic property ($\Sigma\sigma$ or pKa) for the molecules to fit the receptor.

Keywords: acetolactate synthase inhibitors; quantitative structure–activity relationships; CoMFA; sulfonylurea; triazolopyrimidine-2-sulfonamide; herbicides

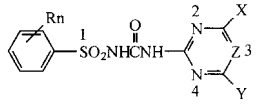
1 INTRODUCTION

Inhibition of essential amino acid biosynthesis in plants is one of the most prominent and attractive principles of herbicidal action.[1] Acetolactate synthase (ALS, EC 4.1.3.18), the first common enzyme in the biosynthetic route to the branched-chain amino acids, valine, leucine and isoleucine, has been identified as the target of action of several structurally distinct classes of compound with high herbicidal activity, namely sulfonylureas, sulfonamides, imidazolinones and pyrimidylsalicylates. These four classes of herbicide were all obtained by traditional screening methods and have been developed as new weapons in weed control. The attributes of low application rates, good crop selectivity, environmental safety and compatibility with the trend towards post-emergence weed control exhibited by these compounds are important characteristics for modern agrochemicals, which have led to the rapid success of ALS inhibitors as herbicidal products and attracted a world-wide research commitment.[2]

It is very interesting that such structurally diverse compounds all act on the same target protein, but unfortunately, so far, no crystallographic data are available for the enzyme-inhibitor complex of ALS, so that it is difficult to rationally design novel ALS inhibitors. Sulfonylureas and triazolopyrimidine-2-sulfonamides are the most important kinds of ALS inhibitor. There are some published studies on structure–activity relationships on these two kinds of ALS inhibitor.[3–6] However, since all of them are concerned with only one series of compounds and most of them are qualitative results, the common features of these two series of ALS inhibitors are not yet clear. Therefore, in a previous paper,[7,8] we reported an investigation on the spatial distribution of benzene rings and fused heterocycle moieties relative to the sulfonyl moieties using X-ray diffraction analysis and quantum chemical calculation, and found many similarities between the two. For the purpose of better understanding the molecular mechanism of action of these two kinds of herbicide, a quantitative analysis was carried out for sulfonylurea and triazolopyrimidine-2-sulfonamide derivatives, combining traditional QSAR analysis with comparative molecular field analysis (CoMFA). To our knowledge, these are the first QSAR and 3D-QSAR studies for structurally diverse ALS inhibitors.

* Correspondence to: G Yang, Institute of Organic Synthesis, Central China Normal University, Tianjin 300071, P R China
E-mail: gfyang@ccnu.edu.cn
Contract/grant sponsor: National Natural Science Foundation of China
(*Received 16 November 1998; accepted 5 May 1999*)

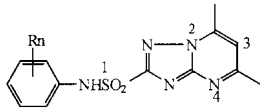
Table 1. Structure, herbicidal activity and physicochemical parameters of sulfonylurea compounds (Series 1)



	Compound				Parameters			pI_{50}								
No	Rn	X	Y	Z	$\Sigma\sigma$	F	$\Sigma\pi$	Obsd	eqn (2)	δ[a]	eqn (4)	δ	eqn(5)	δ	eqn(7)	δ
1	2-$COOCH_3$	CH_3	OCH_3	N	0.50	0.33	0.53	8.24	8.22	0.02	8.30	−0.06	8.15	0.09	8.19	0.05
2	2-$COOCH_3$	CH_3	CH_3	CH	0.31	0.33	1.11	8.11	8.06	0.05	8.00	0.11	8.34	−0.23	8.30	−0.19
3	2-$COOCH_3$	OCH_3	OCH_3	CH	0.69	0.33	−0.05	8.28	8.26	0.02	8.54	−0.26	8.28	−0.00	8.58	−0.30
4	2-$COOC_2H_5$	CH_3	CH_3	CH	0.31	0.33	1.63	8.24	7.93	0.31	7.77	0.47	8.05	0.19	7.95	0.29
5	2-$COOC_2H_5$	OCH_3	OCH_3	CH	0.69	0.33	0.47	8.53	8.13	0.40	8.30	0.23	8.63	−0.10	8.85	−0.32
6	2-$COOC_2H_5$	Cl	Cl	CH	1.19	0.33	1.93	7.10	6.86	0.24	7.29	−0.19	7.26	−0.16	6.87	0.23
7	2-Cl	CH_3	CH_3	CH	0.09	0.41	1.83	8.10	7.81	0.29	7.78	0.32	8.05	0.05	7.93	0.17
8	2-NO_2	CH_3	H	CH	0.71	0.67	0.28	8.30	8.61	−0.31	9.32	−1.02	8.22	0.08	8.42	−0.12
9	H	CH_3	CH_3	CH	−0.14	0	1.12	7.49	7.08	0.41	6.78	0.71	7.48	0.01	7.69	−0.20
10	2-NO_2	CH_3	CH_3	CH	0.64	0.67	0.84	8.37	8.53	−0.16	9.08	−0.71	8.44	−0.07	8.48	−0.11
11	3-Cl	Cl	OCH_3	CH	0.86	0	1.40	7.20	7.24	−0.04	6.90	0.30	7.24	−0.04	7.49	−0.29
12	3-Cl	CH_3	CH_3	CH	0.23	0	1.83	7.17	7.40	−0.23	6.74	0.43	7.17	−0.00	7.09	0.08
13	4-CH_3	OCH_3	CH_3	N	−0.26	0	1.10	6.23	6.82	−0.59	6.69	−0.46	6.19	0.04	6.32	−0.09
14	4-CH_3	OCH_3	OCH_3	CH	−0.07	0	0.52	7.84	7.36	0.48	7.13	0.71	–	–	–	–
15	4-CH_3	CH_3	CH_3	CH	−0.45	0	1.68	6.03	6.15	−0.12	6.20	−0.17	6.07	−0.04	–	–
16	H	OCH_3	OCH_3	CH	0.24	0	−0.04	8.10	7.87	0.23	7.60	0.50	8.00	0.10	7.62	0.48
17	H	OCH_3	Cl	CH	0.49	0	0.69	7.15	7.74	−0.59	7.33	−0.18	7.16	−0.01	7.11	0.04
18	2-$COOC_2H_5$	OCH_3	Cl	CH	0.94	0.33	1.20	7.47	7.60	−0.13	7.85	−0.38	7.40	0.07	7.42	0.05
19	2-$COOCH_3$	CH_3	H	CH	0.38	0.33	0.55	8.20	8.22	−0.02	8.28	−0.08	8.07	0.13	8.27	−0.07
20	2-Cl	CH_3	OCH_3	N	0.28	0.41	1.25	7.88	8.12	−0.24	8.15	−0.27	8.00	−0.12	7.62	0.26

[a] δ, Difference between observed and calculated values.

Table 2. Structure, herbicidal activity and physicochemical parameters of sulfonamide compounds (Series 2)



	Compound	Parameters			pI_{50}								
No	Rn	$\Sigma\sigma$	F	$\Sigma\pi$	Obsd	eqn (3)	δ	eqn (4)	δ	eqn(6)	δ	eqn(7)	δ
21	2-CH_3	−0.17	−0.04	0.34	6.16	5.42	−0.74	5.58	0.58	6.17	−0.01	6.36	−0.20
22	H	0	0	0	6.28	6.28	0	6.01	0.27	6.38	−0.10	6.18	0.10
23	2-Cl	0.23	0.41	0.94	7.27	7.17	0.10	6.85	0.42	7.33	−0.06	7.00	0.27
24	3-Cl	0.37	0	0.92	6.45	5.73	0.72	5.79	0.66	5.77	0.68	–	–
25	3-CH_3	−0.07	0	0.45	5.98	5.65	0.33	5.74	0.24	5.77	0.21	6.09	−0.11
26	2,5-$(CH_3)_2$	−0.24	−0.04	0.79	5.18	4.77	0.41	5.29	−0.11	5.12	0.06	5.29	−0.11
27	4-Cl	0.11	0	0.85	4.48	5.51	−1.03	5.70	−1.22	4.81	−0.33	4.59	−0.11
28	2-NO_2	0.79	0.67	0.81	8.06	8.61	−0.55	7.62	0.44	8.06	−0.00	7.64	0.42
29	2-CH_3O	−0.27	0.26	0.05	6.09	6.69	−0.60	6.41	−0.32	–	–	–	–
30	4-CH_3	−0.31	0	0.43	4.69	5.16	−0.47	5.47	−0.78	4.69	−0.00	4.84	−0.15
31	4-NO_2	1.24	0	0.49	6.29	6.03	0.26	5.57	0.72	–	–	–	–
32	2-Br	0.23	0.44	1.39	7.44	6.79	0.65	6.73	0.71	7.22	0.22	7.31	0.13
33	3-Br	0.39	0	1.36	5.31	5.26	0.05	5.59	−0.28	5.71	−0.40	5.56	−0.25
34	2,6-Cl_2	0.46	0.82	1.88	8.23	7.93	0.30	7.60	0.64	8.46	−0.23	8.39	−0.16
35	3,4-Cl_2	0.48	0	1.77	3.98	4.86	−0.88	5.41	−1.43	4.28	−0.30	4.17	−0.19
36	4-Br	0.15	0	1.36	4.98	5.00	−0.02	5.49	−0.51	4.72	0.26	4.59	0.39

2 MATERIALS AND METHODS

2.1 Test compounds

Sulfonylurea and triazolopyrimidine-2-sulfonamide derivatives used for the analyses are listed in Tables 1 and 2, respectively, which were designed and synthesized according to conventional methods[3,4] by ourselves so as to cover the potency range as widely as possible under restrictions in which the structural variations were mainly made in the substitution pattern in the benzene ring and pyrimidyl moieties. All compounds were purified by repeated recrystallization and their chemical structures were confirmed by NMR spectra and elemental analyses.

2.2 Biological tests

The herbicidal activity of these two set of compounds against rape, *Brassica campestris* L was measured according to the modified method described previously.[9] A set amount of each sample was dissolved in acetone to which a drop of an emulsifier, Sorpol-144, was added. The solution was then diluted with water until it reached the concentration required. The

Table 3. Development of QSAR of eqn (2)

Intercept	$\Sigma\sigma$	$(\Sigma\sigma)^2$	$\Sigma\pi$	*F*	*s*	*r*	*F-test*
7.4533	0.6505				0.6686	0.3852	3.16
7.5508	2.3479	−2.3941			0.4420	0.8053	15.68
7.7849	2.1032	−2.1057	−0.2321		0.4336	0.8255	11.41
7.6049	1.4987	−1.7562	−0.2504	1.3336	0.3481	0.8987	15.74

Table 4. Correlation matrix for variables used to derive eqn (2)

	$\Sigma\sigma$	$(\Sigma\sigma)^2$	$\Sigma\pi$	*F*
$(\Sigma\sigma)^2$	0.6688	1.000		
$\Sigma\pi$	0.0139	0.0214	1.000	
F	0.2443	0.0746	0.0153	1.000

amounts of acetone and the emulsifier were set as low as possible but still sufficient to make a uniform emulsion even at high concentrations. Biological assays were done in vials (diameter = 3.5 cm) containing 4 ml of solution. Five seeds of rape were placed in the solution. The vials were kept at 25 °C, with light of 42 000 lux for 12 h each day. After incubation for 72 h, the shoot length was measured for the five seeds in each vial and averaged. The molar concentration of each compound required to inhibit the shoot elongation to half the length of the control (I_{50} value) was evaluated by the probit method.[10] The I_{50} measurements were repeated for at least three runs and the pI_{50} values were averaged over repeats, the standard deviation being ± 0.20. The activity pI_{50} values of the compounds are listed in Tables 1 and 2, respectively.

2.3 Physicochemical parameters

Hammett's electronic parameters (σ_m, σ_{p+} or σ_{p-}) were taken from literature[11] to represent the electronic properties of substituents. σ_m was used to represent the electron-withdrawing effect of the substituents on the pyrimidinyl moiety of sulfonylureas and *meta* substituents on the benzene rings. σ_{p+} or σ_{p-} was used for the substituents at the *para* position of the benzene rings. For *ortho* substituents, σ_p was taken as the constant for the corresponding *para* substituents. F_{ortho} is the Swain–Lupton–Hansch[12] field-effect constant of *ortho* substituents to delineate the proximity electronic effect overlapping the ordinary effect represented by σ_p.

The determination of logP values of these two series of compounds is inconvenient due to their weak acidity, so the hydrophobic parameter (π) of substituents of sulfonylurea compounds was taken directly from literature.[11] For groups on the benzene ring of triazolopyrimidine-2-sulfonamides, the π values were estimated by eqn (1)

$$\pi(X) = \log P(XC_6H_4NH_2) - \log P(C_6H_5NH_2) \quad (1)$$

where $\log P(XC_6H_4NH_2)$ is the partition coefficient of the corresponding monosubstituted aniline determined for the 1-octanol/water system at 25 °C.[11] For disubstituted compounds, the hydrophobic parameter of substituents is the summation of the π values of each substituent calculated by eqn (1). All substituent parameters used in the QSAR analyses are listed in Tables 1 and 2, respectively.

2.4 Molecular modeling

All computations were done on a Silicon Graphic Indy workstation with the molecular modelling software package SYBYL, version 6.22. To select the initial conformations of compounds, we used X-ray crystallographic coordinates obtained from the literature for reference compounds. Those for compounds **1–19** were modified from the crystal structure of ethyl 2-(4-methylpyrimidin-2-ylcarbamoylsulfamoyl)benzoate [13] (Table 1; Rn = 2−$C_2H_5COO^-$; X = CH_3; Y = H; Z = CH) and those for compounds **20–33** from the crystal structure of 2′,6′-dichlorophenyl-5,7-dimethyl-1,2,4-triazolo-[1,5-*a*]pyrimidine-2-sulfonanilide,[7] (Table 2; **34**). The coordinates of all compounds thus obtained were optimized by molecular mechanics (Tripos field). The atomic charges were calculated using the Gasteiger–Huekel method.

2.5 Superposition of compounds

We hypothesized that the above optimized conformation of the molecules represents the biologically active form. The active conformation of compound **1** in series **1** and that of **34** in series **2** were selected as the reference standards on which those of other compounds in respective series were superposed. As to the

Table 5. Development of QSAR of eqn (3)

Intercept	$\Sigma\sigma$	$(\Sigma\sigma)^2$	$\Sigma\pi$	*F*	*s*	*r*	*F-test*
5.8395	1.0143				1.2218	0.3354	1.77
5.8725	5.6068	−0.7705			1.2549	0.3614	0.98
6.5325	3.0291	−2.0926	−0.7973		1.2612	0.4353	0.94
6.2800	1.7094	−1.1844	−1.1101	3.9084	0.6509	0.8956	11.15

Table 6. Correlation matrix for variables used to derive eqn (3)

	$\Sigma\sigma$	$(\Sigma\sigma)^2$	$\Sigma\pi$	F
$(\Sigma\sigma)^2$	0.6796	1.000		
$\Sigma\pi$	0.1382	0.0929	1.000	
F	0.0888	0.0068	0.1359	1.000

Table 8. Correlation matrix for variable used to derive eqn (4)

	$\Sigma\sigma$	$(\Sigma\sigma)^2$	F	$\Sigma\pi$	I
$(\Sigma\sigma)^2$	0.7057	1.000			
F	0.1725	0.0416	1.000		
$\Sigma\pi$	0.0116	3.71×10^{-3}	0.0156	1.000	
I	0.0416	0.0172	0.0279	0.0122	1.000

superposition between sulfonylureas and sulfonamides, we assigned four atoms to be fitted between the two series, as indicated in Tables 1 and 2, since they both contain a sulfonyl moiety and a pyrimidyl moiety, which were their common pharmacophores according to our previous work.[8,14]

2.6 Correlation analyses by CoMFA

The analyses were done with the QSAR option of SYBYL. The superposed set of active conformers were placed in a lattice of $20\times20\times20$ Å^3 with 2.0 Å spacing where they were superimposed under the conditions mentioned above. The potential energy fields of each active conformer were then calculated at lattice points surrounding the entire molecule. For the calculation of the electrostatic and steric interaction potential at the lattice points, the sp^3 - carbon atom with the charge of +1.0 was used as a probe and the atomic charges in each of the entire molecules were used. The data matrix was analysed by the partial least squares (PLS) method.

3 RESULTS AND DISCUSSION

3.1 Substituent effects on herbicidal activity of sulfonylurea and sulfonamide compounds

Variations in the herbicidal activity of 20 sulfonylurea compounds were analysed using the physicochemical parameters listed in Table 1, giving

$$pI_{50} = 7.6049 + 1.4987\Sigma\sigma - 1.7562(\Sigma\sigma)^2 - 0.2504\Sigma\pi + 1.3336F \quad (2)$$

$$(0.0778)\ (0.4134)\ (0.4379)\ (0.1448)\ (0.4254)$$

$$n = 20,\ r = 0.8987,\ s = 0.3481,\ F = 15.74$$

with the best correlation. The development of this equation and the intercorrelation of variables are shown in Tables 3 and 4, respectively. In this and the following equations, n is the number of compounds, r is the correlation coefficient, and s is the standard derivation. The figures in parentheses under each coefficient are the 95% confidence intervals of the regression coefficient. Equation (2) indicates that electronic factors are the most important physical property in determining herbicidal activity. The negative coefficient of the $(\sum\sigma)^2$ term indicates that variations in the activity are parabolically related to the electronic parameters. The optimum $\sum\sigma$ value in eqn (2) is about 0.50. Besides, from Table 3 we can find that introduction of the F term led to a small but significant improvement in the correlation, suggesting that the *ortho* substituent binding site is electronic in nature. The positive coefficient of the F term indicates the desirability of a proximity inductive effect of electron-withdrawing *ortho* substituents.

For 16 sulfonamide compounds, we obtained the following equation

$$pI_{50} = 6.2800 + 1.7094\Sigma\sigma - 1.1844(\Sigma\sigma)^2 - 1.1101\Sigma\pi + 3.9084F \quad (3)$$

$$(0.1627)\ (1.0874)\ (1.0715)\ (0.4438)\ (0.6697)$$

$$n = 16,\ r = 0.8956,\ s = 0.6509,\ F = 11.15$$

with the best correlation. The development of this equation and the intercorrelation of variables are shown in Tables 5 and 6, respectively. As in eqn (2), eqn (3) indicates variations in the herbicidal activity of sulfonamide compounds are also parabolically dependent on the electronic parameters. The optimum $\sum\sigma$ value in eqn (3) is about 0.72. If considering the electronic property of two methyl groups on the triazolopyrimidinyl moiety, the optimum $\sum\sigma$ value in eqn (3) should be 0.58, which is almost equivalent to that of eqn (2). Besides, eqn (3) also suggests that the electron-withdrawing property of *ortho* substituents on the benzene ring of sulfonamide herbicides is very important for activity, the greater the electron-withdrawing, the higher the activity.

From eqns (2) and (3) we find that the structure–

Table 7. Development of QSAR of eqn (4)

Intercept	$\Sigma\sigma$	$(\Sigma\sigma)^2$	F	$\Sigma\pi$	I	s	r	*F-test*
6.6082	1.1802					1.1951	0.3871	5.99
6.6670	2.6069	−1.9061				1.1460	0.4910	5.24
6.2700	1.1877	−0.9598	2.8787			0.9641	0.6922	9.82
6.5819	1.2490	−0.9930	2.9526	−0.3599		0.9538	0.7115	7.94
6.0102	0.8392	−0.8191	2.7357	−0.4579	1.4179	0.6159	0.8948	24.11

Table 9. CoMFA analyses results

		Conventional			Cross-validated		RC[a]		
Compound	n	s	r^2	F	r^2	OC[b]	Steric	Electro	eqn no
Series 1	19[c]	0.122	0.979	124.056	0.732	5	64.7	35.3	(5)
Series 2	14[d]	0.324	0.955	71.042	0.758	3	84.5	15.5	(6)
Series 1,2	31[e]	0.247	0.972	171.413	0.767	5	65.2	34.8	(7)

[a] Relative contribution.
[b] Numbers of optimal components.
[c] Compound **14** was excluded from the analysis.
[d] Compounds **29** and **31** were excluded from the analysis.
[e] Compounds **14, 15, 24, 29** and **31** were excluded from the analysis.

activity relationships between sulfonylureas and sulfonamides are very similar. Thus, we extented the analysis to include the two set of compounds and obtained the following equation

$$\mathrm{pl}_{50} = 6.0102 + 0.8392\Sigma\sigma - 0.8191(\Sigma\sigma)^2 + 2.7357\mathrm{F} - 0.4579\Sigma\pi + 1.41791 \quad (4)$$

$$(0.1026) \quad (0.5203) \quad (0.5387) \quad (0.4833) \quad (0.1792) \quad (0.2129)$$

$$n = 36,\ r = 0.8948,\ s = 0.6159,\ F = 24.1066$$

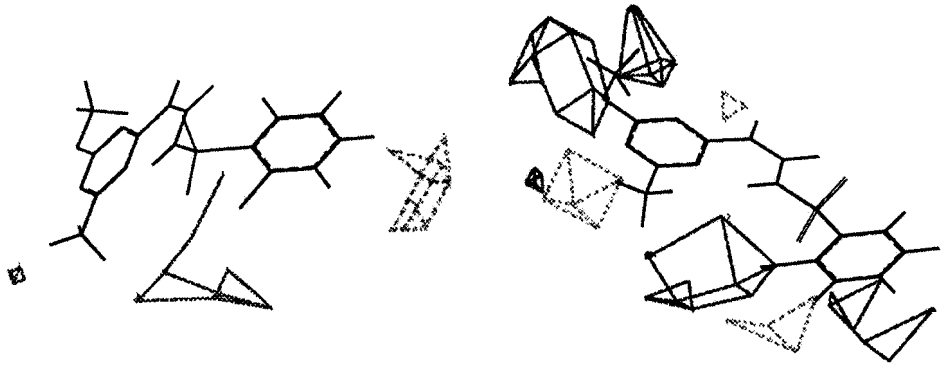
with the best correlation. The development of this equation is given in Table 7 and the correlation of variables in Table 8. I is an indicator variable assigned to be 1 for sulfonylurea compounds, but which is zero for sulfonamide compounds. The coefficient of the I term means that the sulfonylurea compounds have an much stronger activity than sulfonamide compounds with the same electronic and hydrophobic substituents. Equation (4) indicates that the optimum $\sum \sigma$ is 0.51, which is almost equivalent to those of eqns (2) and (3). The herbicidal activities calculated by eqns (2), (3) and (4) are listed in Tables 1 and 2, respectively.

3.2 CoMFA for herbicidal activity of sulfonylurea and sulfonamide compounds

For series 1 and 2 compounds, eqns (5) and (6) were formulated, respectively, as shown in Table 9. In these and the following equations derived by CoMFA, n is the number of compounds, s, r and F are the conventional standard deviation, correlation coefficient and F-test value, respectively OC indicates the number of optimal components, and the cross-validated r is the correlation coefficient from the leave-one-out cross-validation. RC refers to the relative contribution of steric and electrostatic effects to the variations in the activity. In eqns (5) and (6), steric field is more significant than electrostatic field in rationalizing the herbicidal activity variations of the two sets of compounds.

Figure 1 gives the contour maps drawn according to Eqn (5) showing regions in which steric and electrostatic potential fields are either favourable or unfavourable to potentiating herbicidal activity, using compound **20** as example. The zones covered by the contour nets of 'shaded' broken lines in Fig1(a) and the following steric contour maps indicate regions where the submolecular bulk is well accommodated with decrease in activity, whereas the unbroken network zones are regions where the submolecular bulk is favourable, leading to increase in the activity. The zones covered by the nets of 'shaded' unbroken lines in Fig1(b) and the following electrostatic field maps indicate regions where the more negative electrostatic interaction with the receptor binding site increases the activity, whereas those covered by broken lines show regions where the reverse is the case.

Figure 1(a) indicates that steric bulk of the molecular set in the region around the 2-substituents on the



(a) (b)

Figure 1. View of the (a) steric and (b) electrostatic field contour maps for series 1.

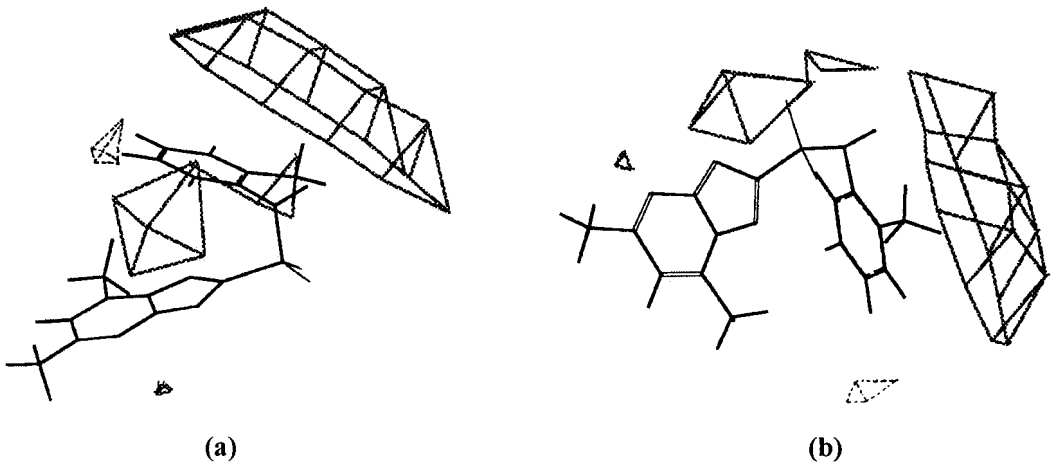


Figure 2. View of the (a) steric and (b) electrostatic field contour maps for series 2.

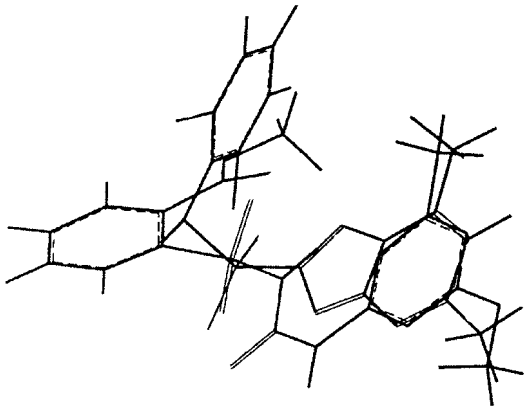


Figure 3. View of the superposition between sulfonylureas and triazolopyrimidine-2-sulfonamides.

benzene ring of series 1 is favourable to herbicidal activity. It also shows that the region at the 4-position of the benzene ring is sterically unfavourable to activity. Figure 1(b) indicates that the pattern of the electrostatic field in regions surrounding the pyrimidyl moiety and the benzene ring is of primary importance in governing the variations in the activity. The region surrounding the 2-position of the benzene ring as well as one of the substitutents of the pyrimidyl moiety is electronegative.

Figure 2 gives the steric and electrostatic contour maps for series 2 compounds, compound **21** being used as example. Figure 2(a) shows that steric bulk of the molecular set in the region around the 4-substituents on the benzene ring is unfavourable to activity. It also shows that a greater steric bulk in the zone around the 2-, 3- and 6-positions of the benzene ring increases activity. Figure 2(b) shows that electron-withdrawing substituents at the 2- and 6-positions of the benzene ring are favourable to activity.

From the above analyses and our previous work,[7,8,14] we can conclude that series 1 and 2 compounds could be bound to a common critical site with similar orientations. Therefore, we explored whether the combined set of series 1 and 2 compounds can be analysed together by CoMFA. Firstly, we examined the overlays of the benzene ring and the pyrimidyl moiety between the two series by conventional atom-by-atom fitting, but all of the overlays obtained were unsatisfactory. In the best result, the position of the sulfonyl moiety and benzene ring seriously deviated from each other when only the pyrimidyl moiety was superimposed, as shown in Fig 3. Therefore, we assigned four atoms to be fitted between the two series, because our previous research work[8,14] indicated that the sulfonyl moiety and fused heterocyclic moiety were their common pharmacophores. The superposition result is shown in Fig 3.

Figure 3 helps to explain the commonality between the herbicidal sulfonylureas and triazolopyrimidine-2-sulfonamides. The sulfonyl moiety is located at the same position relative to the pyrimidyl moiety. The space around the 2-position of series 1 was occupied by the benzene rings of series 2, which suggests the existence of a pocket near the 2-position of sulfonylurea derivatives. Figure 3 also shows that the space near the 6-position of series 2 is occupied by the benzene rings of series 1, and hence should be sterically accessible. Therefore, it was reasonable that com-

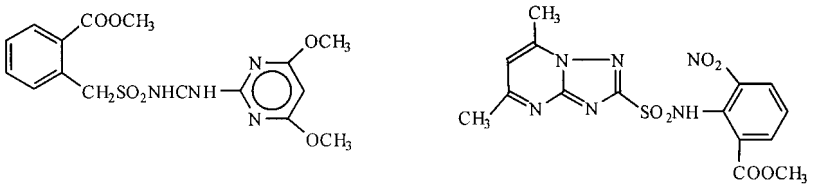


Figure 4. Structure of compounds **37** and **38**.

37 **38**

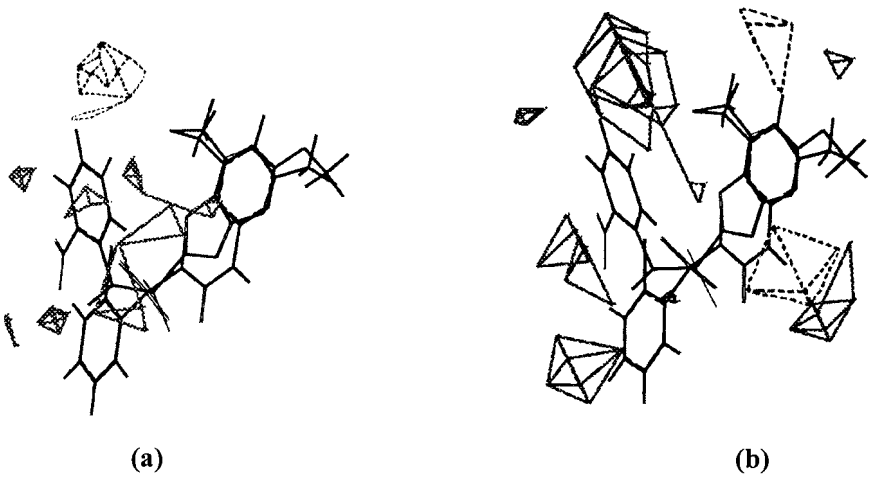


Figure 5. View of the (a) steric and (b) electrostatic field contour maps for series 1 and series 2.

pounds **37** and **38**, whose structures were shown in Fig 4, were developed as highly active molecules.

Based upon the above superposition between the two series, we performed a CoMFA analysis for the combined set of series 1 and 2 compounds to give eqn (7) as shown in Table 9. In eqn (7), only compounds **14, 15, 24, 29** and **31** are not included. Since the activity of compound **24** in series 2 was much higher than expected from eqn (2), it was excluded from the analyses. Compound **14** was also excluded from the analyses because the measured pI_{50} value was much higher than the calculated value according to eqn (7).

Figure 5 shows the steric and electrostatic field maps drawn according to eqn (7). In these figures, features of molecular fields for two individual series seem to be well combined. In Figure 5(a) the sterically prohibited region appears at the 4-position of the benzene ring in series 2. A sterically favourable region is shown around the 2-position of the benzene ring in series 1, which corresponds to the location region of benzene ring of series 2. Figure 5(b) indicates that a negative electrostatic-potential region around the phenyl groups of the two set of molecules is favourable to activity.

4 CONCLUSION

In summary, the CoMFA results herein were in accord with the traditional QSAR analysis using free-energy-related substituent parameters and regression analysis. The combined results revealed that the structure–activity relationships of sulfonylureas and sulfonamides are identical, suggesting that these two sets of compounds have a common binding site on the receptor with similar orientations. According to the QSAR analysis, there is an optimum electronic property for these two sets of molecules to fit the receptor. The negative property of the *ortho* substituent on the benzene rings of the two series is very significant in potentiating activity. These features in the stereo-electronic effects of substituents at the respective positions were nicely reproduced by the CoMFA analysis in terms of the contour maps for coefficients of electronic descriptors at the lattice points, so that not only electrostatically but also sterically permissible or forbidden regions in the molecules could be recognized in a more straightforward manner than with traditional QSAR results. Therefore, combining the traditional QSAR analysis with the CoMFA results, we can conclude that the variations in the herbicidal activity of the two sets of ALS inhibitors are governed by the three-dimensional steric and electrostatic field parameters as well as the hydrophobicity of molecules participating in the interaction with the receptor site.

Furthermore, from the above analyses in which two structurally different series of compounds were dealt with as a single set, additional structure–activity information was extracted that allowed us not only to rationalize the experimental results beyond those for the series of compounds included in the analysis, but also to design and predict novel analogues of higher activity. Indeed, we designed and synthesized a set of novel ALS inhibitors according to the above model, which actually showed a very potent herbicidal activity of the same level as that of compound **34**, which will be reported in detail elsewhere. The fact showed that the above model would be worth further consideration. However, when sets of structurally different compounds are to be analysed by the CoMFA method, the most difficult problem is to find out how to superimpose the molecules. At this moment, traditional QSAR analyses, especially pharmacophore analyses, can provide much important information.

ACKNOWLEDGEMENTS

This project is supported by the National Natural Science Foundation of China. We would like to thank Professor Xiufeng Yang for carrying out the biological evaluations.

REFERENCES

1 Ray TB, Herbicides as inhibitors of amino acid biosynthesis, in *Target sites of Herbicidal Action*, ed by Boger P and Sandmann G, CRC Press Inc, Boca Raton, FL.. pp 105–125 (1989).

2 Stetter J (ed), Herbicides inhibiting branched chain amino acid biosynthesis. *Chemistry of Plant Protection* **10**, Springer (1994).
3 Kleschick WA, Costales MJ, Dunbar JE, Meikle RW, Monte WT, Pearson NR, Snider SW and Vinogradoff AP, New herbicidal derivatives of 1,2,4-triazolo[1,5- *a*]pyrimidine. *Pestic Sci.* **29**:341–356 (1990).
4 Levitt G, The discovery of sulfonylurea herbicides, in *Synthesis and Chemistry of Agrochemicals*. *Part II*, *ACS Symposium* Series 443 ed by Baker DR, Fenyes JG and Stefens JJ, Am Chem Soc, Washington DC. pp 16–31 (1991).
5 Kleschick WA, Costales MJ, Gerwick BC, Holtwick JB, Meikle RW, Monte WT, Pearson NR, Snider SW, Subramanian MV, VanHeertum JC and Vinogradoff AP, 1,2,4-Triazolo[1,5-*a*]pyrimidine-2-sulfonanilide herbicides: influence of alkyl, haloalkyl, and halogen heterocyclic substitution on in-vitro and in-vivo biological activity, in *Synthesis and Chemistry of Agrochemicals*, *Part III*, *ACS Symposium* Series 504 ed by Baker DR, Fenyes JG and Stefens JJ, Am Chem Soc, Washington DC. pp 10–16 (1992).
6 Kleschick WA, Carson CM, Costales MJ, Doney JJ, Gerwick BC, Holtwick JB, Meikle RW, Monte WT, Little JC, Pearson NR, Snider SW, Subramanian MV, VanHeertum JC and Vinogradoff AP, 1,2,4-Triazolo[1,5- *a*]pyrimidine-2-sulfonanilide herbicides:influence of alkoyl, heterocyclic substitution on in-vitro and in-vivo biological activity and soil decomposition, in *Synthesis and Chemistry of Agrochemicals*, *Part III*, *ACS Symposium* Series 504 ed by Baker DR, Fenyes JG and Stefens JJ, Am Chem Soc, Washington DC. pp 17–25 (1992).
7 Yang GF, Yang HZ, Lu RJ and Wang HG, Design, syntheses and biological activity of novel herbicides targeted ALS(III): crystal and molecular structure of 5,7-dimethyl-*N*-(substituted phenyl)-1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide. *Chem. J Chinese Univ (in Chinese)* **18**:1982–1986 (1997).
8 Yang GF, Liu HY, Yang HZ and Yang XF, Design, syntheses and bioilogical activity of novel herbicides targeted ALS(IV): studies on the crystal structure, quantum chemistry and structure–activity relationship of 1,2,4-triazolo[1,5-*a*]pyrimidine-2-sulfonamide Compounds. *Acta Chemica Sinica(in Chinese)* **56**:726–735 (1998).
9 Yang HZ, Zhang YJ, Wang LX, Tan HF, Cheng MR, Xing XD, Chen RY and Fujita T, Quantitative structure–activity study of herbicidal *O*-aryl *O*-ethyl *N*-isopropylphosphoramidothioates. *Pestic Biochem Physiol* **26**:275–283 (1986).
10 Finney DJ, *Probit Analysis*, Cambridge Univ Press, London. p 183 (1952).
11 Hansch C and Leo A, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley-Interscience, New York (1979).
12 Fujita T and Nishioka T, The analysis of ortho effects. *Progress Physic Org Chem* **12**:49–89 (1976).
13 Li ZM, Jia GF, Wang LX, Lai CM, Wang HG and Wang RJ, Syntheses, structure and SAR study on sulfonylurea compounds (II): crystal and molecular structure of *N*-[2-(4-methyl)pyrimidinyl]-2-ethyl carboxylate benzenesulfonylurea. *Chem J. Chinese Univ (in Chinese)* **14**:349–352 (1993).
14 Yang GF, Zhao GF, Lu RJ, Liu HY and Yang HZ, Design, syntheses and biological activity of novel herbicides targeted ALS(V): initial binding model of the herbicidal sulfonylureas and fused heterocyclic sulfonamides with the receptor. *Science In China (Series B)* **28**:283–288 (1998).